76*

Myeloperoxidase promoter polymorphism -465G is associated with more severe clinical expression of cystic fibrosis pulmonary disease

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In cystic fibrosis (CF), the course of the disease varies between homozygous carriers, and this is thought to reflect the contribution of genetic polymorphisms which can exacerbate the associated pulmonary inflammation. We have previously shown that neutrophils of CF patients have higher myeloperoxidase (MPO) enzyme activity. *Aim:* To test whether a functional MPO promoter polymorphism influenced their clinical outcome. The –463G/A polymorphism is linked to differences in MPO expression levels, with the GG genotype associated with increased MPO. The clinical status of 88 patients with CF was evaluated. *Results:* In the group of non-infected CF patients, there is significantly lower FEV or FVC in CF patients with GG than GA genotype. There were more lesions seen on chest radiography in GG than in GA and Shwachman scores were decreased in the group of GG genotype as compared to GA. In contrast, in the group of infected CF patients, there was no significant difference in clinical parameters between GG and GA genotypes. *Conclusion:* MPO genotype significantly influences the severity of pulmonary disease in early stages, prior to development of chronic lung infections, with GG genotype being associated with more severe CF disease. These findings indicate that the level of MPO gene expression influences the pathogenesis of CF, reflecting cellular damage by MPO-generated oxidants.

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77*

Incidence of the IL-8 251 polymorphism and association with lung function in the Northern Ireland CF population

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Interleukin 8 (IL-8) is a pro-inflammatory cytokine fundamental in promoting neutrophil dominated inflammation in CF. The IL-8 251 polymorphism is found in the promoter region of the IL-8 gene, the A allele is associated with increased IL-8 production.
Aims: Frequency of the IL-8 polymorphism was analysed to investigate potential CF related association in the Northern Ireland (NI) population. The relationship between high and low producing alleles of IL-8 with lung function (%FEV_1) was investigated.
Methods: 100 control samples (59% female, 41% male, 19-45y) were chosen at random from the NI population. 101 CF DNA samples (50.5% female and 49.5% male, 15-50y) from the NI population were studied. Analysis of the IL-8 polymorphism was performed using PCR followed by sequence specific oligonucleotide probes.
Results: Genotyping of the IL-8 251 polymorphism revealed that 23 (22.8%) of CF individuals were AA (high producers), 49 (48.5%) were AT (intermediate producers) and 29 (28.7%) were TT (low producers). In the control population 25 (25%) were AA, 45 (45%) were AT and 30 (30%) were TT. There was no significant variation between the two groups for the IL-8 (P=0.926) polymorphism. CF patients homozygous for AA (n=23) and those homozygous for TT (n=49) had significantly lower % FEV_1 than those who were heterozygous AT for the IL-8 allele (AT, 74.9 ± 3.1%, AA, 63.6 ± 4.9%, P=0.04, TT 55.7 ± 4.3%, P=0.001).
Conclusions: These results suggest that patients with CF who are homozygous for the high producing A or low producing T alleles are at a disadvantage to those who are heterozygous as reflected in lower %FEV_1.

78

Association of the group specific component (GC) gene polymorphisms with severe cystic fibrosis lung disease

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Cystic fibrosis (CF), the most common genetic disease in the white population. The major cause of morbidity and mortality for individuals with CF is pulmonary disease due to chronic infection and damaging host inflammatory response. Group specific component (GC) is known to bind with vitamin D, extracellular actin and endotoxin. CG enhances the neutrophil chemotactic activity of complement component 5a (C5a) peptide and C5a des-Arg produced during the activation of the complement cascade. In addition, CG can be converted into a macrophage activating factor. GC may therefore have important influences on the intensity of the inflammatory reactions in the lung.
Method: The study group consisted of 62 Tatars children with severe CF recruited from Republican Children's Hospital (Ufa city, Russia). In control, the DNA samples from 227 unrelated healthy ethnically, age and sex matched individuals were used. The GC gene polymorphisms (Glu416Asp, Thr420Lys) were typed using PCR-RLFP.
Results: Genotype and allele distribution of the Thr420Lys polymorphism was similar among the CF and healthy subjects. Patients with CF showed elevated frequency of the 416 Asp/Asp genotype of GC gene 41.94% compared to control 25,57% ($\chi 2$=5.49 P=0.02; OR=2.1 CI95% 1.11-3.94). The association between GC gene haplotypes and the incidence of severe CF in children was also analyzed. Frequency of the IF/1F haplotype was significantly higher in patients with CF 29.03% compared to control 11.52% ($\chi 2$=10.03 P=0.002; OR=3.14 CI95% 1.49-6.6).
Conclusions: It is suggested that the IF/1F haplotype of the GC play a substantial part in predisposition to severe airway inflammation at children with cystic fibrosis.

79

Alpha 1 Antitrypsin deficiency and Cystic Fibrosis

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Introduction: Cystic fibrosis is a genetic disorder that during its course presents mainly pulmonary and pancreatic manifestations. The correlation between genotype and phenotype is not clear in cystic fibrosis. The severity of disease is not related to the CFTR genotype. Alpha 1 antitrypsin inhibits the proteases that release inflammatory reactions of the plasma. Its most important inhibitory role is it action against leukocytic elastase. As the deficiency of alpha 1 antitrypsin has relevant pulmonary manifestations and is common in the area, we believe that it may be able to modulate pulmonary manifestations in cystic fibrosis patients. *Aims:* The objective of this study was to ascertain the distribution of A1AT genotypes and severity of pulmonary disease in patients with cystic fibrosis. *Methods:* We studied 70 patients; nine (12.8%) were heterozygotes for S or Z allele or compound heterozygotes (SZ). *Results:* No significant differences were found in clinical severity of CF between genotypes of A1AT. No significant differences were found when the patients were separated by the presence or absence of ΔF508 mutation. *Conclusions:* We concluded that the common MS, SS, MZ genotypes of A1AT deficiency that cause mild to moderate protein deficiency are not associated with severity of disease deterioration in Brazilian patients with cystic fibrosis. This is the first study about the relation between Alpha 1 antitrypsin deficiency and Cystic fibrosis made in Brazil.